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CONTEMPORARY STATUS OF THE MOST IMPORTANT PROBLEMS OF HEMATOLOGY
AND PROGRESS IN WORK ON THEIR SOLUTION

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Extensive new experimental and clinical data have been accumulated in the field of hematology during the past 5-6 years. It is understandable that further progress in this important field of medical knowledge is indissolubly connected with an analysis of available data from the standpoint of their profitable use.

We must first turn our attention to one of the most important problems of contemporary hematology, namely that of leukoses.

Luring recent years new experimental proofs of the tumor nature of leukoses have been obtained. Specifically, it has been possible to establish the presence of active blastomogenic substances in the tissues of patients who died of leukoses. These endogenic blastomogenic substances bring about in the majority of experimental animals the development of local and delayed tumors and also of leukoses of various types.

One must emphasize that the blastomogenic activity of some extracts isolated from the tissues of patients suffering from leukosis proved to be higher than that of any known chemically pure cancerogenic substances. The significance of endogenic blastomogenic factors in the origin of leukoses is also confirmed by immunological investigations. By using the method of anaphylaxis with desensitization, it has been possible to establish that specific antigenic properties are exhibited by benzene extracts from the tissues of patients suffering from different forms of leukoses.

Finally, numerous and many-sided cytomorphological investigations have shown that the biological properties of the blood-formation elements of leukosis patients resemble the biological properties of the cells of malignant tumors.

However, the finding that leukoses must be regarded as blastomogenic processes does not solve the problem of leukoses, because the etiology and pathogenesis of blastomata remain unclarified. This leads to the situation that contemporary clinical medicine still does not have at its disposal pathogenetic methods for the therapy of leukoses. While the many-sided therapy of acute leukosis which is being applied contributes to a weakening of some manifestations of the disease, it does not bring about stable changes in the sense that the anaplasia of hemopoiesis is eliminated. The therapeutic measures that are being applied in chronic leukosis can only result in a clinical remission of the disease.

Many data have been obtained recently which speak in favor of the participation of virus-like agents and chemical factors in the etiology of leukoses.

Notwithstanding numerous investigations which have been carried out under experimental conditions and at the clinic, we still do not regard it as possible to draw final conclusions in regard to the origin of leukoses. It is quite apparent that any of the possible concepts in regard to the origin of leukoses may serve as a working hypothesis productive of results.

Further investigations in this field must consist in accumulation of reliable data which have a bearing on the etiological role of viruses, the nature of these viruses, and their antigenic characteristics. In addition to this, it is necessary to continue an intensive study of the etiological role played by endogenic blastomogenic substances and of their physicochemical characteristics and antigenic properties.

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In conducting work on problems of etiology and pathogenesis of leukoses, it is expedient to carry out work on factors which contribute to the development of the leukemic process. In this connection one must devote special investigations to the determination of the threshold, power, and duration of action of radiation that is effective as a leukemogenic factor.

Serious attention must be paid to the creation of experimental models of various forms of leukoses and application of extensive experimental therapy on this basis.

The development of effective methods of the therapy of leukoses is indissolubly connected with a study of disturbances of metabolism in patients suffering from leukosis, particularly the disturbances of phosphorus and purine metabolism, and also clarification of the role played by individual metabolites.

In working on the problem of leukoses, it is expedient to use to wider extent various immunological methods, which are beginning to acquire an increasing importance in the solution of hematological problems. At present, it cannot be subjected to any doubt that leukocytes are carriers of a number of specific antigenic characteristics. It has been proven that leukocytes have the same group antigenic A and B as erythrocytes. From the standpoint of these findings, particular importance must be attached to investigations which deal with the isolation of anti-leukocytic antibodies from the blood of patients suffering from various forms of leukoses. The results which have been obtained are capable of expanding our knowledge in regard to the role played by immunological shifts in the development and course of the leukemic process, particularly as far as aleukemic forms of leukoses are concerned. Clinical medicine has worked for a long time on the development of differentiated indications for the application of various agents that exert an inhibiting effect on foci of leukemic infiltration. This line of research must be expanded by every possible means. At the same time it is necessary to search more persistently for the most favorable conditions which would contribute to a lowering of the toxicity of the therapeutic agents applied for this purpose.

Of great practical importance also is the study of problems pertaining to the resistance developed by leukosis patients to repeatedly applied therapeutic methods in connection with hormone therapy, radiation therapy, chemotherapy, etc. Very important from this standpoint is the investigation of the nature of immunological shifts which develop in response to the application of the therapeutic measures in question.

One must devote more attention to a detailed investigation of the role of immunotherapy (methods involving the use of cytotoxic, antitumorogenic, and antitoxic sera) and of the therapy with hormones (application of adrenocorticotrophic hormone, cortisone, etc.) in the many-sided therapy of leukosis and also to the search for new, more effective, chemical agents which will not exert toxic side effects. According to data published by foreign authors, demecolcin and myleran (1,4-dimethane-sulfonyloxybutane) are the most effective cytotoxic agents available at present, which, at the same time, have the lowest toxicity. Myleran is being used to an increasing extent in the therapy of chronic myeloleukosis. This drug can be applied for a relatively long period of time. After completion of the basic course of treatment with this drug, one must carry out therapy with booster doses to prevent rapid recurrence of the disease. One must expedite the testing of the therapeutic activity of USSR myleran.

Another very important problem of contemporary hematology is that of aplastic and hypoplastic states of hemopoiesis.

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Convincing experimental and clinical results which have been obtained make it possible to state that there are no clear border lines between agranulocytosis and aplastic and hypoplastic anemias; in other words, there is a pathogenetic unity as far as these conditions are concerned.

A very weighty proof in favor of this concept is the fact that in addition to the so-called pure forms of agranulocytosis, there are also unique transitional clinical variants which are distinguished by a pronounced agranulocytosis combined with a gradual development of anemia and thrombocytopenia or either one of these hematological syndromes.

As the basic method for the therapy of plastic and hypoplastic anemias, one regards the systematic transfusion of erythrocytic mass. Lately cationate blood has also been used. This is prepared in the absence of a stabilizer with the aid of ion-exchange adsorbents. This blood approaches in its properties freshly extracted donor blood.

In the treatment of the leukopenic conditions of various origin, including those resulting from the action of ionizing radiation on the body, a new transfusion medium, i.e., leukocytic mass, is being successfully applied. Of importance is the circumstance that under the effect of transfusions of leukocytic mass normalization not only of the number of leukocytes and of the leukocytic formula sets in, but also improvement of the cytological composition of the bone-marrow punctate. Therapy of the patients by other means usually does not bring about beneficial effects as pronounced as this.

Contemporary clinical medicine is accumulating to an increasing extent factual material which confirms that some types of agranulocytosis and some forms of hypoplastic anemia which take an acute course may be reversed.

At present, important data have been obtained relative to the characteristics of shifts to which hemopoiesis is subjected as a result of the effects of ionizing radiation. It has been established, for instance, that in chronic radiation sickness, progressing leukopenia develops in the peripheral blood. This leukopenia is usually combined with neutropenia and thrombocytopenia. A number of patients develop anemia which acquires a macrocytic character; among segmented neutrophils, one encounters gigantic forms which often exhibit a toxic granularity. Changes related to blood formation in the bone marrow are expressed mainly by a delay in the maturation of cellular elements of the leukoblastic and erythroblastic series.

Notwithstanding certain successes achieved in work on this urgent problem, clinical medicine still does not have at its disposal pathogenetic methods for the therapy of aplastic and hypoplastic states of hemopoiesis. It is obvious that the search for new and effective methods of therapy along these lines is connected with the investigation of the etiology and pathogenesis of the diseases involved. More attention should be devoted to research dealing with the role played by ionizing radiation and also with immunobiological shifts that occur in the course of development of aplastic states of hemopoiesis. Specifically, this refers to investigations aiming at the detection in the serum of patients suffering from these conditions of leukolysins, leukoagglutinins, and other antileukocytic antibodies, as well as of antithrombocytic antibodies. This work must be carried on by pursuing an immunochemical line of investigation of the antigenic structure of leukocytes. We are of the opinion that this line of research, which appears very promising both from the theoretical and the practical standpoint, should be considerably expanded and elaborated.

The very interesting investigations of the peculiarities characterizing blood elements from the cytological, biochemical, and cytochemical standpoint and also of the condition and behavior of the organs of blood formation in cases of aplastic and hypoplastic states of hemopoiesis, including those which have developed under the effect of ionizing radiation must be continued.

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Both in the experimental field and at the clinic, work must be conducted on the development and investigation of the therapeutic activity of new agents which exert a hemostatic effect and stimulate erythropoiesis, leukopoiesis, and thrombocytopoiesis. Specifically, special investigations must be conducted on the production and application of a new transfusion medium, i.e., thrombocytic mass. It is advisable to expand work on the role played by leukocytic mass, blood processing with the aid of ion-exchange adsorbents, folic acid, Vitamin B-6, hormone preper blood, and other agents effective in the many-sided therapy of agranulocytosis and aplastic and hypoplastic anemias.

It is well known that many clinical types of leukosis and also aplastic and hypoplastic anemias proceed under the development of pronounced hemorrhagic symptoms. Sometimes, the impression is given that hemorrhages dominate the clinical syndrome of the disease.

At the same time, the origin of the hemorrhagic phenomena which develop under these conditions is not quite clear and clinical medicine still does not have effective methods of therapy which would counteract the hemorrhages. In work on the problems involved, a prominent place must be occupied by the investigation of changes on the part of the coagulating properties of the blood of these patients in the light of new concepts which have been developed lately in regard to the factors that take part in the process of blood coagulation.

The formation of thromboplastin is regarded as the most complex stage in the coagulation of blood. Thromboplastin is an enzyme which brings about the transformation of prothrombin into thrombin and the latter, in its turn, activates the transformation of fibrinogen into fibrin. It has been established that in addition to calcium and the platelet factor, no less than seven other factors take part in the formation of thromboplastin. This includes the antihemophilic globulin and the plasmatic component of thromboplastin.

In addition to the study of the coagulation of blood, much attention must be paid to investigations of the functional condition of the vascular system with the application of the methods of capillaroscopy and oscillography and of tests which determine the permeability of the capillaries.

Among the most timely problems of contemporary hematology is that of hemolytic anemia. Of great practical significance is the classification of hemolytic anemias according to their pathogenesis. This classification is customary in contemporary clinical medicine and involves subdivision into anemias which proceed with a predominant intercellular hemolysis and anemias for which a predominantly intravascular hemolysis is typical. As is known, the first group of hemolytic anemias is subdivided into the congenital type and the acquired type. Immediate observations and observations carried out after the expiration of a lengthy period of time have indicated that splenectomy is 100 percent effective as a therapeutic measure in congenital forms of the disease.

In the therapy of the acquired form of the disease, beneficial results involving action on the cause of the hemolytical process are sometimes obtained by applying transfusions of fresh human plasma, followed by transfusions of erythrocytic mass. The transfusion method of treatment is applied in combination with a prolonged course of treatment with adrenocorticotrophic hormone. However, splenectomy is also often effective in such cases.

It has been established with certainty at present that splenectomy is not indicated in cases of hemolytic anemia which are accompanied by a predominant intravascular hemolysis. In such cases, some therapeutic effect is obtained by applying transfusions of natural human plasma (preferably of the fourth group) and subsequent application of the transfusion of erythrocytic mass. According to the latest data, the development of hemoglobinuria in patients of this type is combined with the activation of one of the globulin fractions (the accelerator),

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which participates in the coagulation of blood. On this finding are based attempts to apply anticoagulants in the therapy of hemolytic anemias which are accompanied predominantly by an intravascular hemolysis. At present, clinicians are subjecting to review some accepted ideas in regard to hemolytic anemias.

A number of investigations has proven the role played by various hemagglutinins and hemolysins in the development of definite pathological processes, particularly as far as hemolytic anemias are concerned. The problem in regard to the pathogenesis of these diseases has been considered in recent years basically from the standpoint of immunology. For instance, it has been established that acquired hemolytic anemia is often combined with autoimmunization and the formation of autoantibodies, which sometimes belong to low-temperature antibodies.

Immunological investigations are acquiring an important role in the differential diagnosis of various forms of hemolytic anemias. For instance, everybody recognizes at present the significance of the special immunological reaction of Coombs, which makes it possible to detect antibodies adsorbed on erythrocytes. This reaction is positive only in cases of acquired hemolytic anemia.

Taking into consideration the immunological pathogenesis of some forms of hemolytic anemia, clinicians must subject to more extensive investigation the role played by various antiallergic agents, particularly adrenocorticotrophic hormone and cortisone, in the therapy of these diseases.

It is advisable to bring further precision to the understanding of those factors which may be of significance in the development of the hemolytic process and to carry out research along these lines. In doing so, particular attention must be paid not only to the role of autoimmune antibodies in the mechanism of the destruction of erythrocytes and to the study of the causes which contribute to their appearance, but also to a detailed investigation of the characteristics of the hemolysis which is observed.

The data which are available testify to the fact that destruction of erythrocytes may take place by intravascular hemolysis with participation of the complement or by erythrophagocytosis. There is either a direct chemical destruction of erythrocytes or intravascular hemagglutination with subsequent formation of substances that exert a lytic effect.

In addition to an extended investigation of the immunological pathogenesis of hemolytic anemias, one must conduct investigations dealing with the role of the virus factor in the etiology of these diseases.

Obviously data accumulated as a result of this work will be of importance in developing effective therapeutic measures. One can assume that a successful development of work on the most urgent problems of contemporary hematology, namely on the etiology, pathogenesis, clinical picture, and character of leukoses and of aplastic (hypoplastic) states of hemopoiesis and hemolytic anemias depends on the utilization of the most modern methods of investigation, which, with every year, find an increasingly extensive application in hematological research. This refers to the isotope method, electron microscopy, and electrophoretic analysis of plasma proteins, luminescence and fluorescence analysis, ultraviolet spectrometry, cytochemistry, chromatography, and various serological and immunological methods. This is, in brief, the status of the most urgent problems of hematology which have not yet been adequately investigated, and these are the methods suggested for the solution of the problems which are very important for public health and with which contemporary hematology is faced.

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